Local Treatments for Cutaneous Leishmaniasis

Mark S. Bailey
Royal Centre for Defence Medicine, Birmingham, United Kingdom

(See the Major Article by Morizot et al on pages 370–80.)

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Cutaneous leishmaniasis (CL) is an infection caused by various species of Leishmania protozoa, which are usually transmitted by the bite of various species of phlebotomine sandflies [1]. It is a “neglected tropical disease” that causes significant morbidity and social stigmatization and also occurs in subtropical regions such as southern Europe and the southern United States. Its clinical presentations and natural history vary considerably, and although nearly all cases will eventually heal spontaneously, this can take more than a year and be complicated by secondary bacterial infections, lymphatic involvement, local recurrences, and mucosal leishmaniasis due to Leishmania (Viannia) braziliensis complex infections in certain New World countries. Laboratory diagnosis requires specialist parasitology and molecular biology techniques, and numerous local and systemic treatment options are available.

Recent studies [2, 3] offer a timely reminder of the value of local (topical or intralesional) treatments for CL, when most research is focused on systemic (oral or parenteral) treatments instead. Morizot et al [2] show how national treatment guidelines and expert advice can optimize the use of simple wound care only or local treatment for a wide range of CL infections in travelers with impressive results. Overall, 62% of cases were treated this way and cure rates within 60 days of starting treatment were 92% for wound care only and 79% for cryotherapy plus intralesional antimony, compared to 60% for systemic treatments. The majority of cases had a good prognosis and were suitable for nonsystemic treatment according to the national guidelines, whereas those with a worse prognosis were more likely to be given systemic treatment, and so there is obvious selection bias. However, some centers would have treated all of these cases with systemic treatments at higher cost and with more adverse effects and so the results remain valuable. Interestingly, no patients seem to have withdrawn due to the transient but severe pain sometimes caused by intralesional treatment (or other forms of cryotherapy) that may dissuade physicians from using such techniques.

Systemic treatments for CL are often preferred for several reasons, including the fact that most new therapies for CL are derived from those used for visceral leishmaniasis, which are inevitably systemic in nature. Local treatments are also more difficult to evaluate due to problems in standardizing the dose given during administration of a topical or intralesional drug. Even when local treatments are known to be effective, there may be problems in the provision of therapies such as intralesional pentavalent antimonial (SbV) drugs (sodium stibogluconate or meglumine antimoniate), cryotherapy, topical paromomycin (aminosidine), and thermotherapy. Overall, our healthcare systems often make it easier to prescribe oral or even parenteral treatments rather than use local treatments such as these.

Although new oral treatments for CL would be welcome, existing local treatments are worthy of further evaluation, and this requires well-designed and adequately powered trials that are standardized to enable comparison with each other. Unfortunately, such studies are often lacking for CL, and even when they are performed, the results may not be reproducible elsewhere due to species differences and also geographic variation in both parasite and patient factors [4, 5]. Hence, the standardized approach used in recent trials of local treatments is just as impressive as the results themselves [2, 3].

Intralesional injection of SbV drugs is the most established form of local treatment for CL, and a variety of volumes and regimens may be used. Numerous studies have been performed in comparison to parenteral SbV treatment or other experimental therapies [6], and in one early study, patients with multiple lesions
agreed to leave some of these untreated as “control lesions” [7]. Responses to intralesional SbV treatment may vary due to differences in the regimen used, the species involved, and other geographical factors. However, cure rates are usually good despite the development of drug resistance by some Leishmania species in certain countries. Intralesional injection requires some skill, produces transient pain, and cannot be used in sensitive body areas or for large lesions. Furthermore, even the small volumes of SbV drugs required may be too expensive for some resource-poor settings.

Cryotherapy for CL is also delivered using a variety of regimens and is often studied in comparison or combination with intralesional SbV treatment. There have been very few adequately powered, appropriately controlled trials of cryotherapy for CL [8], and most Old World studies do not distinguish between L. major and L. tropica infections. Overall, cryotherapy for CL seems to produce cure rates that are superior to spontaneous healing and usually comparable with those for intralesional SbV treatment. The best results seem to occur when cryotherapy and intralesional SbV treatment are combined, but strong evidence for this remains lacking [6]. Cryotherapy is widely used by dermatologists, but can be painful and may be unavailable to infectious and tropical disease physicians who often manage CL, especially in non-endemic countries.

Topical paromomycin treatment for CL has a checkered history that is again complicated by numerous low-quality studies, the use of different preparations and regimens, and results that show species and geographical variation. A meta-analysis in 2007 concluded that in placebo-controlled trials, topical paromomycin appeared to have therapeutic activity against Old World and New World CL, with increased local reactions when combined with methylbenzethonium chloride [9]. However, its efficacy was not significantly different to that of intralesional SbV treatment for Old World CL, and it was inferior to parenteral SbV treatment for New World CL. Some authors have suggested that a nonspecific inflammatory reaction may actually be an important component of the therapeutic response to topical paromomycin, but recent studies using preparations without methylbenzethonium chloride suggest that it can be both effective and well tolerated overall [3]. The next challenge will be to reevaluate these new topical paromomycin preparations and regimens in countries where they have been least effective in the past (such as Iran) and make them more widely available.

Thermotherapy is the most recently developed form of local treatment for CL and has benefited from more standardized regimens and superior trial designs. It can be given as a single session of treatment but requires the use of local anesthetic and prophylactic antibiotics. Thermotherapy has produced cure rates of 48%–83% against CL due to L. mexicana and L. braziliensis in Guatemala [10], L. tropica in Afghanistan [11, 12], L. major in Iraq [13], and L. panamensis and L. braziliensis in Colombia [14]. These results were generally comparable to those of control groups that received intralesional or parenteral SbV treatment, and the duration and adverse effects of treatment were much reduced, although thermotherapy was associated with complications such as blistering and secondary infection. Unfortunately, the cost of radio-frequency thermotherapy equipment means that it is economically most useful in countries where CL is common, but many of these will not be able to afford the initial investment required.

Local treatments have been used less often for New World CL due to concerns about L. (Viannia) braziliensis complex infections leading to mucosal leishmaniasis. However, as the risks of this occurring become more precisely defined [15], it should be possible to use local treatments in a greater proportion of cases. Questions also remain about the role of local treatments for CL when there is evidence of local or lymphatic dissemination. Increased collaboration between researchers and clinicians at an international level should help to answer these questions, and further clinical trials will also be necessary. These must be of high quality, adequately powered, and standardized to make them comparable with each other [16, 17]. They should also be repeated to address possible variation between species, between countries, and between indigenous people and travelers. The clinical trials of local treatments for CL published recently show good progress in this respect.

Note

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References